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Addison's disease; with special reference to etiology

Robert E. Karrer

University of Nebraska Medical Center

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ADDISON'S DISEASE: WITH SPECIAL REFERENCE
TO ETIOLOGY

Presented to the Faculty of the University of Nebraska,
College of Medicine as partial fulfillment of requirements for
the Degree of Doctor of Medicine

By R. E. Karrer

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INTRODUCTION

The trend of development in modern medicine has been marked by the discovery and practical use of hormones of the ductless glands. Particularly thyroxine, insulin, and the parathyroid hormones have become standard substitutes in diseases due to hypofunction of the glands from which they are derived. Curiously enough, Addison's disease, a syndrome connected with destruction and consequent hypofunction of the suprarenal glands, clearly described by Thomas Addison in 1855, has not until recently led to the well-grounded claim of discovery and isolation of the life saving hormone. Therefore, I think it pertinent to review in outline our knowledge of the structure and function of these glands, the hormone and its use in suprarenal insufficiency.

An attempt has been made to give the various etiological factors associated with the disease, their pathology and relative incidence of each.

In conclusion, I might add I have attempted to bring together and include in this brief resume the general proven information concerning this subject.

ANATOMY

The adrenal or suprarenal glands, first described by Eustachius in 1573, are two small flattened, roughly triangular masses of greyish tissue lying in the retroperitoneal space, each in intimate anatomical relation to the kidney on either side. The cut surface resulting from antero-posterior section of the gland is easily divisible grossly into an inner medulla, which stains brown with chromium salts, and outer layer, the suprarenal cortex which does not. The cortex can in turn be indistinctly divided on microscopic examination into three concentric layers, according to arrangement of their constituent cells, into the inner zona reticulosa, the middle zona fasciculata, and the outer or peripheral zona glomerulosa (29).

In the evolutionary scale as well as in embryological development the two main divisions of these structures have been shown to have different origins. No tissues comparable to them have been exclusively demonstrated in the bodies of invertebrate animals. In at least some of the fishes they remain as separate structures throughout life. In the human embryo, the medulla is derived from chromaffin cells lying in the sympathetic ganglia of the coeliac plexus; that is, it is ectodermal in origin. The cortex, on the other hand, originates as ingrowing buds of peritoneal mesothelium covering the genital ridge and is of mesodermal origin. Portions of the suprarenal anlage may become separated from the parent

gland and form accessory suprarenals which usually consist wholly of cortical tissue. These may be found in the region of the main gland or in the retroperitoneal space, remote from it, occasionally imbedded in the organs, or they may follow the migration of the gonad to the pelvis or scrotum. They occur occasionally in man, in a small percentage of dogs and cats, and perhaps most frequently in rabbits and white rats (3).

The foregoing facts make it obvious that, although in man and the higher mammals the suprarenal cortex and suprarenal medulla are intimately associated anatomically, they should be considered as separate and distinct organs embryologically, structurally and as will be pointed out, physiologically.

PHYSIOLOGY

Addison's observations that the diseases of the suprarenal gland led almost invariably to a fatal outcome indicated their functional activity was necessary to life. Brown-Sequard shortly thereafter (1856) removed the glands from various animals, obtained postoperative survival periods of only nine to thirty-seven hours. Numerous subsequent investigators including Rogoff and Stewart, have reached similar conclusions. The latter workers, however, state that Brown-Sequard only happened to be right since his survival periods were so short, death in his animals probably resulting from post operative shock (94).

In 1894 Oliver and Schafer (62) discovered that extracts of the suprarenal medulla produced a definite rise in blood pressure when injected into animals. In 1901 Takamine (92) and Aldrich (2) working independently isolated in crystalline form the active principal of the medulla. Because this substance (adrenalin or epinephrine) in pharmacologic dosage gives rise to elevation of blood pressure, hyperglycemia, increased contractions of voluntary musculature, and other striking physiological effects, undue importance was given to the physiological effects of that given off to the blood stream by the medulla in the live animal, and the conclusion was reached that the medulla is the part essential to life. It has been demonstrated, however, that epinephrine injected into the blood stream at the rate at

which it is normally secreted by the glands (0.000225 mg. per kilo per minute) (83) actually depresses the blood pressure slightly rather than raises it (42). It has, in fact, been suggested that it is a toxic excretion product, and that one of the functions of the medulla is to so control its flow into the blood that it will never reach a sufficient concentration to be harmful. It has, moreover, been repeatedly found in animal experimentation that, when animals are bilaterally adrenalectomized, if accessory adrenals which are purely cortical are present (as in many rabbits and rats), or if a piece of one gland consisting solely of cortex is left with an intact blood supply, these animals survive indefinitely and enjoy good health (82) (69). It is further claimed that if the cortex is removed, leaving the medulla intact, death results as after total suprarenalectomy. Furthermore, there is a growing number of reported cases of Addison's disease in which at autopsy the cortex alone was found destroyed while the medulla was in good condition (30) (14) (6). In at least one instance, in which there were no symptoms during life, the medulla was found wholly destroyed while the cortex was intact (6). At any rate, the majority of authorities concur in the opinion that, whatever may be the function of the medulla, it is not one which is indispensable, and that it is the cortex which is to be considered essential to the maintenance of health and life.

The death of bilaterally adrenalectomized animals

and the clinical entity known as Addison's disease, must, then, depend upon the partial or total ablation of the suprarenal cortex. The elucidation of the etiology of this disease and the pathogenesis of its symptoms must be dependent upon a study of its physiology. Unfortunately only too little is known of this. What little is established is as follows:

The cortex is closely related to the development of the sexual organs (73). It arises from the mesoderm in common with the gonads. Certain cases of sexual precocity are associated with hypertrophy of the cortex. It becomes hypertrophied during pregnancy and after castration. It is ill developed in sexual deficiency. There is said to be considerable similarity between the cells of the cortex and those of the corpus luteum. Rogoff and Stewart (70) have shown that the postoperative survival period is definitely prolonged in bilaterally adrenalectomized animals which are operated when in heat or during pregnancy.

Two main theories have in the past been current regarding the mode of action of the adrenal cortex; 1. that it exercises a "detoxicating" function and 2. that it elaborates an internal secretion or hormone. The first suggested by the fact the cobra venom was rendered innocuous by mixture with an emulsion (2).

However, experiments designed to show an increased susceptibility of adrenalectomized animals to various toxic

drugs have yielded indefinite or negative results. The evidence at present is overwhelmingly in favor of the second theory, and, as will be described below, active cortical extracts have been obtained by several investigators.

Rogoff and Stewart (70) have obtained average post-operative periods of survivals in bilaterally adrenalectomized animals of eleven days in cats and more than one week in dogs. They consider the dog the best experimental animal for investigation of the suprarenals. Rogoff states, in describing the postoperative course of these animals: "Untreated adrenalectomized dogs continue in good health up to about two or three days preceding death, regardless of the period of survival. During the period of good health the animal cannot be distinguished from any healthy unoperated dog....The period of decline begins with the development of anorexia, and this is usually preceded by an aversion to food rich in fat... Vomiting frequently occurs, becoming bilious in character and blood is commonly found in the stools, as the animal rapidly declines. During this period the animal generally becomes apathetic and somnolent, but rarely has more than transient asthenia. However, events progress somewhat rapidly at this stage and within the ensuing day the animal becomes much more somnolent and decidedly asthenic. As the symptoms develop, the blood pressure falls... Coma is present sometimes for a number of hours before death. Frequently there are symptoms referable to the nervous

system. Hallucinations develop, the animals stare as if in alarm and this is associated with fits of yelling and racing about in the cage." At postmortem they found congestion of the pancreas with a well defined gastro-enteritis. Rogoff (69) states that he has seen pancreatic congestion also in human cases of fulminating character and implies that this is the probable reason for the aversion to fats which is seen both in experimental animals and the clinical cases. We readily see that the symptoms of Addison's disease which results from a slowly developing, perhaps only partial, destruction of the cortex, differ in some respects from those of acute total suppression of suprarenal function which occurs in these experimental animals.

The investigators suggest that the function of the hormone of the cortex is to exert some regulatory action upon metabolic processes and the vital organs in general, the break resulting from the absence occurring in the gastrointestinal tract. They consider the manifestations of Addison's disease and the clinical symptoms in operated animals are due to an intoxication resulting from the lack of this regulatory influence (82).

This conception is made plausible by the facts that the postoperative survival period is much prolonged in dogs (70) and the patients have been rescued from crisis, by the intravenous administration of normal saline or glucose solution. The obvious inference is that the toxins are diluted

or washed out of the body in this way.

ADDISON'S DISEASE

Previous to the middle of the nineteenth century little or nothing was known of the suprarenal glands except their anatomy. Ideas advanced regarding their physiology, that they served to hold up the stomach, that they strengthened the nervous plexus which touches them, that they act as a filter to make the blood more fluid, etc., impress one as absurdities in the light of present day knowledge. Addison concluded the preface to his article, "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules" with the paragraph: "There are still, however, certain organs of the body, the actual functions and influence of which, hitherto entirely eluded the researchers, and bid defiance to the united efforts of both physiologist and pathologist. Of these the least remarkable are the suprarenal capsules, and it is as a first and feeble step toward inquiry into the functions of these organs suggested by pathology, that I now put forth in the following pages." The article itself is devoted to the presentation of eleven cases of what had previously been known as idiopathic anemia with post mortem findings, preceded by a summary of the outstanding clinical features (1) quoted from Wakefield and Smith (94). To use Addison's own words in describing the disease, "the leading and characteristic feature to the morbid state to which I would direct attention are, anaemia, general languor and debility, remarkable feebleness of the heart's action,

irritability of the stomach, and a peculiar change in color in the skin, occurring in connection with a diseased condition of the suprarenal capsules" (20).

The oldest record of an illness which in all probability was one of Addison's disease is reported by Maranon (58). This writer found an account of the illness of a young priest which was reported and recorded in the "Historia primitiviary exacto monasteria del Escorial". The priest's illness occurred in 1554-1557 and dates from fright during a storm when lightning struck the monastery. The illness was one of melancholia, emotional instability, and the white color of the skin changed to a sad pallor. The patient lingered along, from bad to worse, and finally died after an illness which lasted three years.

Addison's work must be regarded as the beginning of modern thought and knowledge on the suprarenals; his work was the first work which connected abnormal states of these structures with a definite clinical picture. In fact we have at the present time progressed only a little farther than his original opinion that the symptoms are produced by an interruption from any cause of the functional activities of the adrenal bodies.

The diagnostic syndrome of Addison's disease contains four main symptoms.

1. Muscular asthenia is often the first and certainly the most constant manifestation of the disease.

The outstanding complaint is often that of extreme lassitude. Some patients may have considerable temporary muscular power, but show a more or less complete lack of resistance to fatigue.

2. Pigmentation is perhaps the most striking feature. This is an exaggeration of the normal pigmentation of the cells of the Malpighian stratum of the skin, and is quite variable both as to distribution and intensity. It shows a predilection for, or is more intense in, those areas which are normally more deeply pigmented, such as the axillary folds and areolae of the nipples, which are subjected to friction or pressure, and which are exposed to the rays of the sun. It may be as generalized as a sunburn or may occur in patches which vary widely in size. Most characteristic is pigmentation of the face and mucous membrane of the mouth. It varies in color from a faint brown to a dense bronze or even negroid hue.

3. Vascular hypotension is present in the great majority of cases and is often quite marked. The systolic pressure has reached the low level of fifty millimeters of mercury. There are a few cases, however, in which repeated observation fails to reveal a blood pressure which can be considered abnormally low.

4. Gastro-intestinal symptoms are practically a constant accompaniment of the disease. Anorexia is a marked feature of many cases. Tympanities is often troublesome. Uncontrollable vomiting or diarrhea or both occur sometimes.

All these lead to loss of weight and sometimes to extreme dehydration (16).

Various nervous symptoms may form a part of the symptom complex, the most common of which is headache.

There is no laboratory determination, no test of metabolism which has been demonstrated to be of any considerable help in the diagnosis of this condition. Blood counts do not show any constant change, Addison's impression was to the contrary that an anemia is constantly present. Basal metabolic rate determinations show some tendency to low readings, but not more so than can be accounted for by the presence of inanition and dehydration. Glucose tolerance tests in at least some instances show a low curve, indicating a high tolerance for sugar. It is said many patients have an excessive per twenty-four hour excretion of creatine when on diets known to have a low content of this substance. The high blood nitrogen values seen in the crisis and terminal stages of some cases are probably to be interpreted as relative renal failure due to hypotension and dehydration. Gastric hypoacidity or even anacidity is present in the majority (16).

The course of the disease, which varies in duration from a few weeks to three or four, or exceptionally, seven or more years is often characterized by repeated remissions and exacerbations. These latter may reach a degree of severity sufficient to justify the term "Addisonian Crisis". In a

"crisis" the condition of the patient becomes so serious that he is justly considered to be in imminent danger of death. The asthenia, gastro-intestinal symptoms, dehydrations, and perhaps the hypotension, become extreme. The disease almost invariably has resulted fatally (16).

INCIDENCE

Addison's disease is relatively rare. In 1924, 363 cases were reported in 1,173,990 deaths from all causes in the registration area of the United States (30). A scrutiny was undertaken of the records of 12,000 consecutive post mortem examinations at the Leeds General Infirmary (1910-1930) with regard to the occurrence of Addison's disease. Nine fully attested cases were found, all of them with definite disease of the suprarenal glands (38). During the past 30 years of the University College Hospital, London, there have been 23 cases of Addison's disease examined post mortem out of a total of 5915 necropsies (6). Osler (63) saw only seventeen cases of Addison's disease in the course of 21 years. Boothy and Sandiford (13) recorded but thirteen Addisonians in a series of 2417 cases studied at the Mayo Clinic.

In other words, the cases presenting the classic signs of adrenal disease as described by Addison, are most infrequently encountered (30).

It is a common observation that Addison's disease is seldom seen in sanatoriums for tuberculosis. This is probably due to the fact that the extra suprarenal tuberculous lesions in Addison's disease are usually small and healed or clinically latent. A history of an old tuberculous process occurring many years before the onset of the symptoms of Addison's disease is often obtained. It is likely that in

many patients treated in sanatoriums the symptoms of Addison's disease develop many years after discharge. There is no doubt that cases of bilateral suprarenal tuberculosis occur in sanatoriums, but it is likely that in many cases the symptoms therefrom are obscured by symptoms of advanced pulmonary tuberculosis, such as weakness, low blood pressure and gastro-intestinal disorders (30).

AGE

Addison's disease is rare in the first years of life, only 3.45 per cent occur in the first decade. The incidence increases rapidly and reaches a maximum in the fourth decade. Following this period, there is a rapid decline in the incidence of the disease. Primary contracted suprarenal glands (atrophy) are rare before the third decade. The maximum number of cases also occurs in the fourth decade of life (30).

HEREDITY

Proved cases of Addison's disease in more than one member of a family are exceedingly rare. Fahr and Reiche (23) quoted from Guttman (30) reported symptoms of Addison's disease in three brothers of a family of twenty-three, eleven of whom died in youth. One, 23 years of age, was examined post mortem and atrophy of the suprarenal glands was found. The other showed marked pigmentation of the skin and weakness. Fleming and Miller (26) described a case of undoubted Addison's disease in a woman who had four children with symptoms of weakness, brownish pigmentation of the skin and occasional attacks of diarrhea. Unfortunately further information as to the duration of these cases cannot be found in the literature, and it is impossible to state with certainty that these were true Addison's disease. Pigmentation of the skin of some other member of the family was noted in the cases reported by several observers. These cases are questionable, as insufficient data are at hand to establish the diagnosis with certainty. Lewin (54), quoted from Guttman (30), in his entire study found three cases in which the disease had been considered hereditary.

It is doubtful, therefore, whether heredity plays an important role in the genesis of the disease, although it cannot be denied that in rare instances there is an hereditary tendency.

It is believed by some that a constitutional pre-

disposition may be a hereditary factor in this disease, but that other intercurrent factors are necessary before the disease results (30).

SEX

Of the total number of reported cases, 313, or 64.57 per cent, occurred in males, and 172, or 35.43 per cent in females. The predominance of male over female is evident not only in the reports of cases in which the diagnosis was established at autopsy, but also in the clinical reports. However, in the case of primary contracted suprarenal glands, the females predominated over the males in the ratio of 1.6 to 1. In the cases of tuberculosis of the suprarenal glands the predominance of males over females, as shown by the post mortem records, can be accounted for partly by the fact that, in most laboratories, there are more post mortem examinations performed on adult males than on adult females. At the University of Minnesota, there are 1.5 times as many on adult males as on adult females; however, in the post mortem reports of tuberculosis of the suprarenal glands the predominance of males over females is 2.88 to 1. The clinical reports, which are free from this error, show 1.59 males to 1 female (30). Lewin's (54) statistics quoted from Guttman (30) give the ratio of male to female as 3.2 to 1.

RACE

Seven cases of Addison's disease in the Negro were reported from 1900 to 1929. Increase in depth of pigmentation of the skin and pigment flecks in the mucous membrane of the mouth were noted. The color change is often notable, the patient turning from brown to jet black. Pigmentation of the mucous membrane, an important diagnostic sign in the white race, is of little importance in the colored race, since pigment flecks often occur normally. Because of the difficulty of detecting pigmentary changes in the Negro, it is probable that the disease is more prevalent than one is led to believe by the case reports. One case has been reported in a mulatto. Reports of Addison's disease in Jews are rare. Statistics are not available for the yellow races. Numerous case reports indicate that it occurs in the Japanese (30).

TUBERCULOSIS

It is generally stated that tuberculosis of the adrenal glands accounts for from 80 to 90 per cent of cases of Addison's disease. The tuberculous process appears to start either in the medullary or in the mid cortical portion and then advance toward the periphery (17).

Three possible routes of infection of the suprarenal glands have been considered by various authors, viz., intrauterine, hematogenous and lymphogenous. Ellasser (21) quoted from Guttman (30) concluded that in cases of isolated suprarenal tuberculosis, the infection must find its explanation in a congenital infection followed by a long period of latency. There is much evidence opposed to this theory. Although it is well known that bacilli may be present in the blood stream and tissues without producing tissue reactions, it is highly improbable that the bacteria remain latent for many years. The low immunity of the tissues of infants furnishes a fertile field for the development of bacilli, and infections in the fetus would not be long becoming disseminated. That tuberculosis is rarely transmitted through the placenta is indicated by reports of such cases. Hubschmann (43), quoted from Guttman (30), was of the opinion that transmissions via placenta is usually accompanied by tuberculosis of that tissue. He considered only those cases congenitally transmitted in which the symptoms of the disease occur shortly after birth, rarely later than the third week

of life.

There is little evidence in the observation at necropsy that infection takes place via lymphatic channels. Involvement of adjacent lymph nodes is not infrequent, and may be considered as an extension from the lesion in the suprarenal gland. The position of the primary lesion in the majority of cases is such that extension through the lymphatic vessels is improbable (30).

The anatomic relationship of lesions in the lung and lesions in the suprarenal gland strongly suggests the hematogenous route. Schwarz (78) quoted from Guttman (30) in a study of sixty-five cases of tuberculosis of the suprarenal glands, both unilateral and bilateral, found lesions of the same age or older in the lungs in every case. In almost half of his cases the lungs were the only other organs involved. The remaining showed hematogenous involvement of other viscera. Schwarz concluded that the suprarenal infection is secondary to lesions in the lung and that the infection is carried by the blood stream. It has been pointed out that, in Addison's disease, the lesion is seldom primary, and that it is associated in most cases with active lesions elsewhere in the body. There are cases, however, in which primary lesions healed, and a small number in which no lesions can be found outside the suprarenal glands. These cases have led many to regard the infection as congenital or hereditary. However, in the light of recent knowledge of

tuberculosis, this assumption is unnecessary. It has been shown that apparently healed foci may harbor the bacilli.

Hubschmann (43) also held that these areas are capable of giving off bacteria into the blood stream without local acute exacerbation of the lesion. It has also been shown that bacillemia may occur in patients harboring lesions that anatomically are difficult to find. Such hidden foci in parts of the body other than the lung, in many cases, must be considered. It is also possible that extensive bilateral lesions in the suprarenal glands may produce a state of immunity in the rest of the body, so that lesions elsewhere tend to remain localized and to heal. The frequent association of hematogenous infections of other viscera, such as the spleen, kidney, liver, epidymis, etc., also is strong evidence favoring a hematogenous origin of the lesion in the suprarenal glands.

Colton (17) also believes in the hematogenous origin of the infection. He states, "Adrenal tuberculosis is usually secondary to lesions elsewhere in the body, and is usually haematogenous in origin. The lungs seem to have the call as to the original focus in about 50 per cent of the cases, and hidden or active foci in other parts of the body in the remainder."

A number of hypotheses have been advanced to explain the occurrence of extensive, apparently isolated, bilateral tuberculosis of the suprarenal glands found in Addison's dis-

ease. Wiesel (97), quoted from Guttman (30), and others held that the suprarenal glands are predisposed to infection by a hypoplastic condition of the chromaffin system which is associated with status lymphaticus. Bauer (7), quoted from Guttman (30), cited an analogous situation in which hypoplastic organs are the site of tuberculosis, but such reports are few compared with the frequency of hypoplasia. The inconstancy of lymphatic and thymic hyperplasia in cases of tuberculosis of the suprarenal glands throws doubt on the etiologic significance of status lymphaticus. Lowenthal (57), quoted from Guttman (30), recently pointed out the meagerness of evidence on which Wiesel based his conclusion that the chromaffin tissue is hypoplastic in his so-called cases of status lymphaticus. In the majority of cases of primary contracted suprarenal gland, the medullary tissue shows little or no deviation from the normal, the cortex being the main site of the lesion.

Hansemann (31), quoted from Guttman (30), regarded the local predisposition of the suprarenal gland to tuberculosis as the result of a low fat content of the tissues. Schur (77), quoted from Guttman (30), considered that the suprarenal glands are made more susceptible to infection by injury as a result of a previous acute infectious disease.

While it is a common observation that a patient dates his first symptoms to the attack of influenza, of grip, or less frequently of typhoid fever, of diphtheria, etc., it

is improbable that these diseases predispose the suprarenal glands to tuberculosis.

Colton (17) believes an exacerbation of a previously quiescent lesion anywhere in the body may be brought on by intercurrent illness of any kind, exposure, overwork, overplay or any of the multitudinous causes of reactivating tuberculous lesions from which the blood may bear the tubercle bacilli to any part of the body, including the adrenals.

Keilty (48) states "The question as to whether a strain of tubercle bacilli with a predilection for the adrenal is only a supposition, and on the other hand any chemical combination which the adrenals might have had in attaching the tubercle bacilli to the particular site would, it seems to me, be decided possibility. The complete absence of tuberculosis elsewhere in the body, in the presence of such active lesions as found in the adrenals, offers a further field for study. That the organisms had any predilection for the adrenal gland is more certainly ruled out by the fact that when inoculated into a guinea pig they produced in duplicate the usual experimental tuberculosis."

From an analysis of forty-nine cases of tuberculosis of the suprarenal glands, there is evidence that the infection is first unilateral and later bilateral. It is found that unilateral lesions are seldom extensive and but rarely destroy the entire gland. When bilateral, one gland often shows more recent and less extensive involvement than the

opposite organ. It seems therefore that the same conditions apply here as in the kidney and the eye. The exact mechanism of the predisposition, however, is not yet clear. The extensive alterative and exudative changes in the glands is strongly suggestive that the inflammation is allergic. It is probable that this allergic state is the result of the sensitization of one organ to the tubercle bacillus or its products, as the result of previous primary infection of the opposite organ (30).

Colton (17) has found there is a tendency to involvement of both glands as in other paired organs in the body, one first becoming affected, and later a metastasis to the other, probably, he thinks aided by lowered resistance or an allergic reaction.

The structural changes in the suprarenal gland in tuberculosis are fairly typical. In the majority of cases, the substance is replaced completely by semiconfluent caseous nodules, varying in size from a few millimeters to 2 or 3 cm. in diameter, separated by septums of grayish white connective tissue. Between the caseous nodules, a tissue of reddish brown color with fine, grayish nodules is often present. Microscopic sections through the areas often show active miliary tubercles. Conversion of the entire gland into a shell containing soft, cheesy or semifluid contents is described. Normal tissue is usually present in the form of a thin rim of yellow cortical substance, or a portion of in-

tact medulla and cortex may be present at one or more poles of the gland (30).

Microscopically, the glands are replaced for the most part by large homogeneous confluent caseous masses. The reaction about these varies considerably. Most commonly areas of caseation are well walled off by fibrils. In other portions of the same gland, the process may be more active, the reaction consisting of marked epithelioid cell formation, giant cells and wide zones of lymphocytic infiltration. Less frequently, the proliferative reaction is lacking, and wide areas of caseation are bordered by partially necrotic parenchymal cells and leucocytes.

The medulla is frequently completely destroyed, whereas large portions of the cortex may remain. This indicates that the medulla is less resistant to the infection than the cortex.

Fibrosis of the capsule and the surrounding tissue may be extensive. Included in the fibrous mass may be seen sympathetic nerves, blood vessels and small groups of sympathetic ganglions. Hyperplastic intimal changes in the smaller arteries are common. The veins are not infrequently the site of thrombosis (30).

The cases caused by tuberculosis do not differ materially from those due to other causes. However, it is generally agreed that those with tuberculosis die more quickly than those with primary contracted adrenals (atrophy).

ATROPHY

Suprarenal atrophy is not an uncommon cause of Addison's disease as is shown by the following table.

Investigator	Place	No. of cases of Addison's disease	No. of cases showing atrophy of adrenal gland
Brenner (14)	Birmingham	8	3
Conybeare and Mills (18)	London	29	7
Harbity (32) quoted from Susman (85)	Norway	22	2
Hedinger (37) quoted from Susman (85)	Germany	15	1
Philpott (65)	Michigan	14	1
Snell and Rountree (81)	Rochester, Minn.	30	4
Susman (85)	Manchester	6	5
	Total	127	23

Of 124 cases, 23 or 18.5 per cent showed atrophy of the adrenals, a figure which appears somewhat higher than might be expected. The high figure is mainly due to the results obtained by three observers, in the 43 cases of Brenner, Conybeare and Mills, and Susman 35 per cent are atrophies and they account for 15 of the 23 cases of atrophy or two-thirds of the total number. In the United States 44 cases included 5 cases of atrophy, or about a third of the number obtained in England. In Norway, 22 cases included 2 of atrophy, a similar result to that obtained in the United States. In Germany, the proportion is 1 in 15. In other words, England:

U. S. A.: Norway: Germany :: 15: 5: 4: 3.

This percentage corresponds with that of other observers. Brenner (14), in reviewing 68 cases of Addison's disease, found 13 cases of atrophy or 19 per cent.

Atrophy of the adrenal gland was apparently recognized quite early. Coupland, according to Barker (4), in 1885 reported a case of clinical Addison's disease in which both suprarenal glands were found to be markedly atrophied.

Microscopically, the suprarenal capsule in cases of atrophy show thickening and infiltration with lymphoid cells. The cortex is greatly reduced in amount and in some sections is practically missing. It consists of a number of islands separated by thick strands of dense vascular fibrous tissue infiltrated with lymphoid cells. The cortical cells are loosely and very irregularly arranged. They are mostly greatly enlarged, though some of them are no larger than the cells of the normal suprarenal cortex which they closely resemble. The nuclei are usually small and vesicular, though sometimes they are large and hyperchromatic, and some are pyknotic. Some cells have two nuclei. Most of the cells contain yellowish-brown pigment granules. All stages of degeneration of the cells can be seen. The medulla is usually normal in amount and seems normal, apart from a few small areas of fibrosis and lymphoid infiltration around the central vein (14).

The process seems to be similar in all cases, but

some authors have thought it to be inflammatory, others of atrophic origin.

There are several possibilities as to the nature of the process.

1. That it is a congenital hypoplasia of the glands, according to Neusser and Wiesel (61), quoted from Brenner (14), especially of the chromaffin system and associated as Hart (33), quoted from Brenner (14), thinks with status thymico-lymphaticus. This view seems to be untenable. The process first attacks the cortex, not the medulla or the chromaffin system. The thickening of the capsule, increase in fibrous tissue, and round cell infiltration, are all in favor of an acquired, not a congenital process. Moreover, in many cases the stages of actual destruction of the cortical cells, with areas of regeneration and hyperplasia, are clearly visible. For these reasons it may be concluded that the atrophy is not due to congenital hypoplasia (14).

2. That the atrophy is due to chronic inflammation. Simmonds (80), quoted from Brenner (14), says that tuberculosis is the commonest cause of atrophy, and that the tuberculous process may heal so completely that it is impossible to find the cause of the fibrosis. But in most cases of suprarenal atrophy there is no tuberculosis elsewhere in the body, or there is an old healed lesion at the apex of a lung. This does not absolutely disprove the tuberculous origin of the diseases, since in frank caseous

suprarenal tuberculosis there may be no obvious primary tuberculous focus elsewhere in the body. Simmonds (80) also considered the possibility of a syphilitic lesion elsewhere in the body as it had previously been mentioned in two cases, including Barlow's (5), quoted from Brenner (14), in which there was a gumma of the kidney.

3. That the process is a simple atrophy of the cortex and later of the medulla, with attempts at regeneration. The cause is obscure. As Butzke (9), quoted from Brenner (14), points out, the usual cause of atrophy, such as disuse, over-use, pressure, neurotrophic disturbance, and circulatory lesions, can rarely be shown to have acted in causes of suprarenal atrophy. Nevertheless, it is possible that over-use may be a contributory cause. Jaffe (46), quoted from Brenner (14), found that if, in rats, excessive work is thrown on the accessory cortical suprarenals by the removal of the main glands, such rats often die after months of ill health, and the accessory suprarenals show interstitial fibrosis, vacuolation and distortion of cells. This description recalls the appearances in cases of human cortical suprarenal atrophy, and suggests the possibility that the changes may in part be due to exhaustion atrophy of a cortex previously deficient, owing to some other cause (14).

Again, in a few cases, such as those of Simmonds (80) and Fahr and Reiche (23), quoted from Brenner (14), there were lesions in the suprarenal vessels, but it is more

likely that they were due to the same cause as the atrophy, or were due to the atrophy, rather than that they caused the atrophy. Many cases of severe vascular lesions of the suprarenals have been described. Hirsch and Capp (41) describe a case of thrombosis of the suprarenal veins resulting in death in six weeks. Areas of necrosis of cortical cells were present and the medullary cells were shrunken and pyknotic. Similar cases have been described by Ellis (22) and others. In most cases there were areas of necrosis and hemorrhage, especially in the cortex. But in none of these cases had the process lasted long enough for chronic changes to occur. Henschen (40), quoted from Brenner (14), described a case in which one suprarenal was converted into a large blood cyst. The pathological process in all these cases is quite different from that in cases of atrophy, but in a few cases the changes show some resemblance to those in atrophy. Thus Veit (93), quoted from Brenner (14), describes a case of Addison's disease in which one suprarenal was absent and the vein of the other was thrombosed. The medulla was necrotic and the cortex showed areas of necrosis, fibrosis, and atrophy, with areas in which the cells were enlarged. Furita (28), quoted from Brenner (14), describes a case of infective endocarditis with many emboli in branches of the suprarenal arteries. The medulla was normal. The cortex showed fibrosis, round cell infiltration, much necrosis and atrophy of the parenchymal cells, and small adenoma like areas of regeneration. Such

changes as these might conceivably represent the first stage of suprarenal atrophy, but, since there were no vascular changes in most of the cases of atrophy described, it is improbable that this is true in most cases.

Block (12), quoted from Brenner (14), thinks that the symptoms of Addison's disease are due to lack of adrenalin. He suggests that the round cells present in atrophic suprarenals are not lymphocytes but sympathicogonia which have proliferated in order to compensate for the lack of adrenalin, and have thus caused atrophy of the cortex. But the cells have neither the appearance nor the arrangement typical of sympathicogonia, and they have been identified by Paunz (64), quoted from Brenner (14), as derivatives of the reticulo-endothelial system. They are often confined to the cortex, the medulla being free from them. Block's (12) suggestion is therefore not warranted.

None of the theories put forward give a satisfactory explanation of these cases of suprarenal atrophy. It seems there is a slow necrosis of the cortex with destruction of most of the cells. Those which remain undergo compensatory hypertrophy and multiply to form adenoma like nodules, the cells of which are then attacked by the same process; or perhaps part of the further degeneration is due to exhaustion atrophy of the remnants of cortex. The process may later spread to the medulla. The fact that the process primarily involves the cortex of both suprarenals and

any accessory cortical tissue which may be present suggests that a toxin with a special affinity for suprarenal cortex may be at work. It is possible that the toxin may be of bacterial origin. In scarlatina and in diphtheria the medulla is practically normal, while the cortex shows oedema and loss of lipoid. In other severe infections the cortex shows oedema, loss of lipoid, and vasculature and even necrosis of its cells, with an increase in vascular connective tissue. Since few people go through life without having a severe infection of some sort, it is possible that one of these may be the prime cause of atrophy, but there is no definite evidence as to this. Neither is there any evidence that the cause is a poison produced by faulty metabolism (14).

Wells (95) believes the similarity of the changes in "suprarenal atrophy" and "acute yellow atrophy" of the liver suggest a similarity in etiology. It seems well established that the latter depends on extensive damage to the liver cells by toxic agents, which may be of most varied character and origin, having only in common the capacity to destroy a large portion of the liver cells without producing a lethal injury in other tissues. In some cases, the toxic agent is definitely known, in more it is not, and in some cases it seems probable that the severity of the damage depends rather on an unusual susceptibility of the liver cells to the poison than on the amount or quality of the poison. In each case, a selective necrosis of the functional epithelial

cells occurs with a minimum amount of injury to other cells, followed by absorption of the dead cells, attempts at regeneration and compensatory hypertrophy by the survivors, and death from loss of the specific functioning cells of the organ. The fact that in this type of Addison's disease both suprarenals are usually involved in the same way and to about the same degree supports the view that the changes depend on some agent entering through the circulation.

There is no evidence to substantiate any of these theories and all the authorities conclude that the cause is really quite unknown.

Regardless of which of the two major diseases, atrophy or tuberculosis, the symptoms do not greatly differ. Those with tuberculosis are said to die more quickly than those with primarily contracted adrenals (atrophy) (17).

AMYLOIDOSIS

Amyloidosis is infrequently associated with the cause of Addison's disease. Autopsy findings in a number of cases at the University Hospital of Michigan show that amyloid deposit in the adrenal gland occurs in a fairly large percentage of those subjects showing a generalized amyloidosis.

Philpott (65), in a review of 2,550 autopsy cases, reveals fourteen which can be classified under Addison's disease. Only one of these cases was caused by amyloid infiltration.

The literature shows only five other cases. All five showed marked amyloid deposits in the adrenals and have definite diagnostic proof of this disease being present.

A recent paper by Hunter (45) discusses in detail the clinical and pathological findings in those cases previously reported. With reference to the adrenals, pathologic findings are fairly constant. The gross appearance shows the gland of normal or slightly increased size, increased firmness, yellow, white or grayish color, the cut surface giving a slight waxy appearance. Microscopic examination shows the amyloid in greater amounts in the cortex; the zona reticularis and fasciculata are most affected, while the zona glomerulosa is only slightly involved. The medulla has only small deposits which are chiefly surrounding the blood vessels. All cases have a bilateral involvement of the adrenals.

In a series of 100 tuberculous patients that came

to autopsy, 18 cases of amyloid disease were found. Of these 14 or 78 per cent showed also amyloid infiltration of the adrenals involving mainly the cortex (15).

The percentage of amyloid infiltration is much higher than the incidence of the disease. This is probably due to the fact that in amyloidosis there does not occur complete destruction of the cortical cells, but merely an atrophy and loss of some of them. The remaining cells are presumably capable in most cases of carrying on their necessary function (59).

McCutcheon (59) reports a case of Addison's disease associated with widespread amyloidosis which involved the cortex of both adrenals. The amyloidosis apparently resulted from a large hypernephroma. Hunter and Rush (45) report a case showing the cardinal symptoms of the Addisonian syndrome. Extensive pulmonary tuberculosis and marked renal insufficiency were very evident. The latter proved to be due to amyloidosis of the kidneys.

Schlesinger (75), quoted from Guttman (30), and Schuttz (76) also report cases of Addison's disease associated with amyloidosis.

Clinically, the diagnosis is often difficult because of the symptoms of the underlying condition.

SYPHILIS

Syphilis of the suprarenal gland with the symptoms of Addison's disease was present in only one case proved at autopsy by Sezary (79), quoted from Guttman (30). In this case, symptoms of asthenia and pigmentation followed shortly after primary infection, and death occurred four months later. The suprarenal glands showed sclerosis and gumma formation. Spirochetes were demonstrated. Clinical reports are more numerous. Schaffner and Howard (74) described a case which they thought clearly demonstrated a syphilitic suprarenal lesion which vastly improved by antisyphilitic treatment. The diagnosis was based on the favorable response of this patient to antisyphilitic treatment. Since spontaneous remissions are often seen in cases of Addison's disease, the response to antisyphilitic treatment cannot be accepted as adequate proof of the syphilitic nature of the lesion.

MISCELLANEOUS

MALARIA: Lellis (53) reports a case of Addison's disease in a malarial patient. The extreme weakness and bronzing developed in a young man a few weeks after an acute malarial infection. The Addison's symptoms completely disabled the patient, but at the fourth month from the first onset of malaria, epinephrin was given systematically, and in three weeks the earning capacity was quite restored. Quinine had not been taken after the epinephrin was started. The successful outcome Lellis believes testified that the suprarenals had been injured by the malaria in the first place, and the functional insufficiency had persisted after quinine had cured the malaria. Under the epinephrin, the suprarenals were given a chance to recuperate, and clinically normal conditions were soon restored.

Fulchuero (27) presented three patients with malaria who apparently had typical symptoms of Addison's disease. These patients improved under the treatment for malaria, and epinephrin, the Addison syndrome subsided, except for the pigmentation. This persisted practically unmodified. The diagnosis was based on the favorable response of these patients to antimalarial treatment. Since spontaneous remissions are often seen in cases of Addison's disease, the response to antimalarial treatment cannot be accepted as adequate proof of the malarial nature of the lesions.

DENERVATION: Rogoff (67) reports a case of Addison's disease following adrenal denervation. In this case an attempt had been made to benefit a diabetic individual by denervating the adrenal glands. The history indicates that this syndrome was superimposed on preexisting diabetes by surgical intervention with the adrenal glands. The surgical manipulation apparently resulted in occlusion of the blood vessels and degeneration of the adrenal cortex. Such degeneration has been demonstrated to occur experimentally by Rogoff (68). When the adrenal blood supply is interfered with in animals subjected to operations creating serious circulatory disturbances they develop acute, subacute or chronic adrenal cortical insufficiency comparable or identical with Addison's disease. This case illustrates the serious danger of attempting adrenal surgery for the correction of various ailments supposedly associated with adrenal function.

VASCULAR LESIONS: Bilateral massive hemorrhage into the suprarenal glands is not infrequent in adults, following acute septic conditions. Death is usually rapid and often accompanied by symptoms simulating peritonitis. Unilateral thrombosis of the suprarenal vein is not infrequently encountered, but is usually symptomless. Bilateral thrombosis of the suprarenal veins associated with Addison's disease was reported by Straub (84), Veit (93) and Kovacs (50), quoted from Guttman (30). In Straub's case, symptoms of pigmentation and weakness developed in seventeen days following thrombosis.

Veit reported a case in a widow, aged 50, in whom symptoms appeared in the course of from four to five weeks. In Kovacs' case the lesions are of longer duration, the symptoms, however, being manifested only a few days before death.

In the early stage, the organ is usually enlarged and dark in color. The medulla is first involved and later the cortex. The central part is replaced by a dark red, firm tissue. In the later stages (Korvacs), the organ is shrunken, the capsule is thickened, and there is partial organization of central detritus which contains abundant cholesterol and blood pigment.

Anemic infarction was present in a case described by Furuto (28). Destructive cortical lesions resulting from multiple articular emboli in the course of an ulcerative endocarditis was seen on microscopic study. Macroscopically, the organ appeared normal.

FATTY DEGENERATION: Loeper and Olliver (56) report a case of what seemed to be fatal Addison's disease in a woman, age 31. At necropsy both suprarenals presented primary fatty transformation, analogous to similar changes that have been observed in other glands and the thymus. It was evident that the changes were connected with congenital malformation of the suprarenals; weakness, arterial hypotension and pronounced bronzing were the clinical features of the case. There were no signs of inflammation or tuberculosis of the suprarenals. The cause of the fatty degeneration is entirely un-

known.

MALIGNANCY: Poynton and Lond (66) describe two cases of pulmonary carcinoma which, during their lifetime, showed symptoms which enabled them to diagnose Addison's disease. Autopsy showed primary carcinoma in both cases with secondary metastasis to the suprarenal glands. Bicknell (10) reports a case of Addison's disease due to involvement of the solar plexus, and not the capsule by malignant growth. At autopsy there was no evidence of malignancy, tuberculosis, or atrophy but a large mass of carcinomatous glands pressed directly on the coeliac plexus. The cases reported by Poynton and Lond can be compared with any other destructive lesion of the suprarenal gland. The latter case appears to be very similar to that reported by Rogoff, the pressure of the malignant growth causing degeneration of the nerves to the gland with secondary atrophy.

THE RELATIVE IMPORTANCE OF THE CORTEX AND OF THE MEDULLA
IN THE PRODUCTION OF SYMPTOMS OF ADDISON'S DISEASE

That the symptoms of Addison's disease are due to a more or less complete destruction of the suprarenal gland is widely accepted. However, the relative importance of the cortex and that of the medulla are widely disputed. The symptoms of the disease are believed by some to be due entirely to the destruction of the cortex; by others, entirely to the destruction of the medulla, while some believe that the destruction of both cortex and medulla is responsible for the symptoms of the disease.

From his early studies Wiesel (97), quoted from Guttman (30), concluded that the symptoms of Addison's disease are due to loss of chromaffin tissue. He based his conclusion on a study of five cases of Addison's disease in which the medulla was markedly diseased and the chromaffin tissue entirely lacking. He considered of special significance another case in which destruction of the suprarenal gland occurred without symptoms of Addison's disease, but in which the extra-suprarenal chromaffin tissue was intact.

Karakascheff (47), quoted from Barnard (6), was directly opposed to this theory, believing that the cortex is solely responsible for all the symptoms. He pointed out that in Wiesel's cases of extensive destruction of the gland without symptoms of the disease, accessory cortical nodules were present, the significance of which Wiesel failed to

emphasize. Further, he stated, that since the chromaffin organs along the course of the sympathetic ganglions normally undergo retrogressive changes shortly after birth, he failed to understand why their absence in cases of Addison's disease should be considered of significance. Karakascheff based his conclusions that the cortex was mainly responsible for symptoms of Addison's disease on a study of two cases of atrophy in which the cortex was mainly involved and in which the medulla was normal.

Some writers are of the opinion that destruction or impairment of function of both portions is necessary before the complete syndrome is produced. Falta (24), quoted from Guttman (30), regarded the low blood pressure, low blood sugar, adynamia, mononucleosis and pigmentation as the result of a lessening of the function of the medulla; the gastrointestinal symptoms (vomiting, diarrhea), and coma as dependent on the destruction of the cortex. Wiesel (96), quoted from Brenner (14), in 1913, altered his former view and stated that asthenia and low blood pressure were the result of an inadequacy of the chromaffin system, whereas the nervous symptoms, the cachexia and lethal end were due to failure of the cortex. Fenwick (25) stated that as the skin changes occur sometimes after, or sometimes before, the onset of the constitutional symptoms, and sometimes not at all, it follows that they cannot be of identical origin. He therefore concluded that the constitutional symptoms are of medullary

origin, and that the pigmentary changes are of cortical origin. Fahr and Reiche (23), quoted from Guttman (30), also believed that pigmentation is due to cortical insufficiency, but they did not state which part is responsible for the other symptoms. They concluded from a study of five cases of primary contracted suprarenal glands in which anatomically the medulla showed little or no change, that functional impairment of the medulla cannot be ruled out.

There are apparently two reasons for these conflicting opinions: 1. too hasty conclusions are reached from the clinical and pathologic observations of a single case of Addison's disease, and 2. experimental evidence offers conflicting views as to the functions of the suprarenal glands. The extreme variability of symptoms, particularly those of blood pressure and pigmentation, could easily lead one to erroneous conclusions from a study of a single case or a small group of cases. A correlation was made by Guttman (30) of the outstanding clinical symptoms and changes in the suprarenal glands of all the available cases in an effort to determine whether or not any relationship exists between the symptoms and the relative degree of destruction of the cortex and the medulla.

A comparison of the blood pressures in cases of suprarenal tuberculosis with that in primary contracted suprarenal gland was made; as in the former, the medulla is mainly involved, and in the latter, the cortex is the main seat of

involvement. Among the cases of tuberculosis of the suprarenal glands there were sixty-five in which the blood pressure readings were compared with twenty-three cases of primary contracted suprarenal gland. The mean, maximum, minimum and standard deviations were recorded. The difference between the means was 2.47, which is less than one times their probable error, so that this difference cannot be considered as significant. Normal and even increased blood pressure were reported as frequently for tuberculosis of the suprarenal glands as for primary contracted suprarenal glands. However, in both groups, the systolic pressure was below normal and about equally decreased (30).

It is clearly evident, therefore, that the blood pressure is not dependent on the relative degree of destruction of one or other of the two layers of the suprarenal glands. Normal and even high pressures were observed in cases in which the medulla was totally destroyed, and markedly reduced pressures were seen in cases with normal medulla.

In an effort to determine further whether the extent of involvement of the medulla, on one hand, and of the cortex, on the other, influences in any way the nature of the symptoms, thirty cases of primary contracted suprarenal gland were compared with tuberculosis of the suprarenal gland. These cases were picked at random from cases in the literature. Here again it was seen that the frequency of the major symptoms differs but slightly and cannot be considered of any

significance (30).

These cases offer strong evidence to show the major symptoms of Addison's disease are not dependent on the degree either of cortical or medullary destruction. All symptoms may be strongly manifested in cases in which the medulla is normal, and there is no apparent difference in cases in which the medulla is normal, and there is no apparent difference in intensity of symptoms in cases in which the medulla is slightly involved or normal and cases in which the medulla is markedly involved.

It is therefore evident that following the destruction of the medulla alone, the cortex may function and prevent symptoms of the disease. It is also clear that all symptoms of the disease may be clearly manifest in cases in which the cortex is destroyed and the medulla is intact. However, it cannot be denied that for the normal function of the gland, the two parts are essential and act synergistically. There are several reasons why this may be so. Bredle (11), quoted from Rountree and Ball (73), has stated that the peculiarity of the vascular supply and the ontogenetic and phylogenetic development of the suprarenal glands suggests a functional relationship between the cortex and the medulla. Landau (51), quoted from Guttman (30), has stated that, in the development of the gland, the infolding of the cortex suggests a functional relationship between the cortex and the medulla, as in this way a larger surface of the cortex is

brought into apposition with the medulla. Cramer (19) claimed to have traced a functional relationship between the cortex and medulla by using stains by which he was able to trace the functional activity of the gland. Hartman and Hartman (35), using the calorimetric test, the inhibition of intestinal contraction and the denervated iris tests, found that epinephrin is present in the cortex.

It is probable, therefore, that an anatomically intact medulla may not function normally when the cortex is the seat of marked destruction. It is also likely that the extreme variability of symptoms observed in cases of primary contracted suprarenal gland may be due to the varying degree of disturbance in the synergism of the cortex and medulla. However, if this relation is shown not to exist, one must fall back to the theory that the destruction of the cortex alone is responsible for all the symptoms of Addison's disease.

TREATMENT

GENERAL: The treatment of a patient with Addison's disease should include rest, mental and physical relaxation, a light nutritious diet preferably high in carbohydrate, adequate fluid intake, and various symptomatic measures. Any accompanying or underlying disease (e.g., tuberculosis) must of course receive proper consideration and treatment. Dehydration may be primary from hormonal deficiency or secondary to continuous vomiting or diarrhea. Fluids should be administered intravenously and subcutaneously as saline or glucose solutions. They should be used promptly and freely in crisis; this often saves the life of the patient (16). Sodium chloride by mouth is often helpful. Loeb and Atchley (55) believe patients with Addison's disease require from 10 to 15 gm. of salt daily in addition to that of their diet. The amount varies with the severity of the disease and the most valuable therapeutic guide next to the determination of the sodium content of the blood serum, is the sense of well-being of the patient and the level of the blood pressure.

SPECIFIC: Attempts at organotherapy have been made since Addison's day, with indecisive or negative results. In 1920 Rountree (72) at the Mayo Clinic instituted a plan of treatment in the case of the late Dr. A. L. Muirhead (60) of Creighton University, consisting of the administration of adrenalin by hypodermic, rectum, and mouth to tolerance,

together with whole gland or dried cortex by mouth, with, for a short time, brilliant results. Dr. Muirhead, however, died in less than a year (72). This procedure, since known as the Muirhead regimen, has been the best plan of treatment available to the profession in general. However, the statistics of its chief exponent, Rountree (72), show that it is of only temporary value in but little more than half the cases treated; in about one-sixth of the cases the improvement lasted for three to seven years; in the remainder the treatment seemed to be harmful. Rountree regards it as only palliative in the therapy of Addison's disease.

The hope of a more efficient treatment seems to lie in the development and manufacture in commercial quantities, of an active hormonal extract of the cortex. At present the only reliable criterion of activity of cortical extracts is the rigid one that by the administration of the substance the postoperative life span of bilaterally suprarenalectomized animals shall be definitely prolonged beyond the maximum for the untreated controls. At the present time three independent groups of investigators claim to have produced an extract which answers this requirement.

In 1927 F. A. Hartman (36) and his colleagues obtained a substance which they call cortin by precipitation with sodium chloride from a watery extract of cortex. Injections of cats twice daily with this substance prolonged the average survival period to 27.4 days as compared with

five to six days for their controls. Subsequently (June, 1930) (34), the method of preparation was changed to an alcohol and ether extraction which provided an extract of a desired concentration, 50 gms. fresh cortex per cubic centimeter.

In February of 1928, Rogoff and Stewart (70) reported the preparation of an adrenal extract which prolonged the survival period, when administered intravenously to adrenalectomized dogs, definitely beyond that of their numerous untreated controls. They have subsequently named this product interrenalin. In May of 1929, they reported improvement in seven cases of Addison's disease under treatment by interrenalin by mouth (71). This improvement appeared about two to four weeks after the beginning of treatment and consisted of improvement in appetite and strength, gain in weight, control of diarrhea, moderate rise in blood pressure, and lessening of pigmentation.

The preparation with which the most outstanding results have been reported, both in animals and man, is that of Swingle and Pfeffner. In December, 1929, they reported the extraction from cortex tissue with alcohol and benzene of a liquid fraction which they demonstrated to be effective in prolonging the lives of bilaterally adrenalectomized cats (88). Later, by means of redistribution through acetone, petroleum ether, and alcohol, they were able to further eliminate inert substances and obtained an aqueous extract

which satisfied the criterion of potency (87). With this aqueous extract they brought back to normalcy operated cats showing early symptoms of hypoadrenia, and even rescued animals from the last stages in which they were prostrate and in imminent danger of death (90). By filtration through permutit the solution is practically freed of adrenalin (91) (to a concentration of one part in 1,500,000 or less) and the product can be given intravenously without danger from this source.

Rountree and Greene (73) reported a series of seven cases treated by them at the Mayo Clinic with the hormone of Swingle and Pfeffner. The immediate improvement resulting from the daily intravenous injection of fifteen to twenty cubic centimeters of the extract was rapid and dramatic. In a recent summary of their experience with this treatment, they state that of the twenty-two cases of Addison's disease the immediate results were excellent in seventeen; six died, three while under treatment; and three gave unsatisfactory or no response.

They summarize the clinical changes observed with the treatment as follows: "(1) disappearance of anorexia, nausea, vomiting and of pain; (2) development of hunger and return of normal gastro-intestinal activity; (3) relief from fatigue and improvement in sleep; (4) increase in strength and endurance; (5) increase in weight; (6) decrease in pigmentation; (7) change in mental attitude with an access

of hope and euphoria; (8) increase in blood pressure, although slight and secondary; (9) resumption of normal functions and desire to work and (10) increased resistance to infection, surgical procedure and drugs" (73).

Attempts have been made to cure patients with Addison's disease by the transplantation of adrenal cortex. Beer and Oppenheimer (8) reported the results in two such cases. The first patient obtained some temporary improvement following transplantation, so that it was thought advisable to repeat the procedure several weeks later. The patient's condition improved so strikingly that the authors believed it justifiable to assume that the patient was suffering from Addison's disease and that the transplant "took".

The authors did not make any definite claims for this operation as a curative measure. As a final suggestion, which the authors have had no opportunity to try, would be the combined use of adrenal cortical transplants and the adrenotropic fraction of the anterior pituitary extract, to stimulate both the transplanted tissue and whatever viable adrenal rest the host may possess.

Wilder (98) observed that the majority if not all of patients with Addison's disease continue to require a larger than normal supply of sodium chloride even when receiving cortical extracts. They suggested that something more than cortical extract is necessary to make good the hormone deficiency in Addison's disease. This in turn sug-

gested the probability of secondary deficiencies. That secondary deficiency of the anterior lobe of the pituitary body may be a factor has been given special consideration.

They used an extract of the anterior lobe of the pituitary gland which was said to contain the growth promoting and thyreotropic hormones. They report two cases treated with extract of the anterior pituitary gland in conjunction with cortin and sodium chloride. Both of these patients were less sensitive to deprivation of sodium chloride in periods when they were receiving anterior lobe pituitary extract, in conjunction with other treatment. Also, both patients were distinctly stronger when receiving the anterior lobe pituitary extract. The observations suggest that sensitiveness to restriction of sodium chloride in Addison's disease may depend, in part at least, on secondary insufficiency of the anterior lobe of the pituitary gland and that anterior lobe pituitary hormone may be employed with advantage in the treatment of this disease as a supplement to cortin (98).

The treatment of Addison's disease has not been entirely satisfactory. Patients in crisis have been resuscitated but their lives have not been prolonged indefinitely and although a substantial number of them have been brought from the state of invalidism to a reasonable degree of health, none of them has been restored to full efficiency.

SUMMARY AND CONCLUSIONS

Addison's disease is relatively rare. Both sexes are affected. Males are more frequently affected than females. Heredity can be considered a factor only in rare instances. The age incidence of primary contracted suprarenal gland and that of suprarenal tuberculosis are approximately the same.

Tuberculosis of the suprarenal gland is seldom seen in the absence of tuberculous lesions elsewhere in the body. The primary focus is usually in the lungs and ordinarily it is not recognizable clinically. Tuberculosis of the adrenals accounts for between 80 and 90 per cent of the cases. Infection takes place through the blood stream. The medulla appears more susceptible than the cortex to the infection, and it is usually completely destroyed. Remains of the cortex can be made out microscopically in most cases. The disease is progressive and characterized by periods of healing and periods of exacerbation. Healing is rarely observed.

Primary contracted suprarenal gland is a disease of unknown etiology and causes the majority of the remaining 10 to 20 per cent of the cases. The pathologic changes indicate that the condition is primarily a slow necrosis involving the cortical cells and leading finally to their disappearance. Partial function is maintained by regeneration in the form of small adenoma-like nodules of cortical cells. There is no evidence that the lesion is due to infection or

to the toxic products of lesions elsewhere in the body.

Any lesion destroying the adrenals may cause Addison's disease but aside from atrophy and tuberculosis they are relatively rare and unimportant.

Conclusions as to the relative importance of the cortex and medulla cannot be drawn from a study of a single case or a small group of cases, as the symptoms of the disease are extremely variable. Evidence is lacking that the symptoms occurring in primary contracted suprarenal glands differ from those occurring in tuberculosis of the suprarenal glands. No appreciable difference in the symptomatology can be noted with varying degrees of destructions of the cortex and medulla. Available experimental and clinical evidence points to the fact that the adynamia, gastro-intestinal symptoms and low blood pressure are due to an accumulation of toxic substances subsequent to suprarenal destruction. The lethal end is due to cortical failure. All symptoms may be present in cases with anatomically normal medulla; however, a functional disturbance of the medulla as the result of disturbance in synergism of the cortex and medulla cannot be denied.

The treatment has not been satisfactory. Patients in crisis have been prolonged indefinitely and although a substantial number of them have been brought from a state of invalidism to a reasonable degree of health, none of them has been restored to full efficiency.

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